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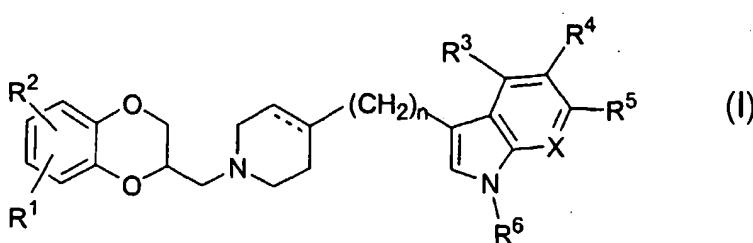
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(54) Title: ANTIDEPRESSANT AZAHETEROCYCLYMETHYL DERIVATIVES OF 2,3-DIHYDRO-1,4-BENZODIOXAN

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(57) Abstract: Compounds of the formula (I), useful for the treatment of depression and other conditions such as obsessive compulsive disorder, panic attacks, generalized anxiety disorder, sexual dysfunction, eating disorders, addictive disorders caused by ethanol or cocaine abuse and related illnesses.

**ANTIDEPRESSANT AZAHETEROCYCLYMETHYL DERIVATIVES OF
2,3-DIHYDRO-1,4-BENZODIOXAN**

5 This invention relates to antidepressant azaheterocyclymethyl derivatives of 2,3-dihydro-1,4-benzodioxan, to processes for preparing them, methods of using them and to pharmaceutical compositions containing them.

Background of the Invention

10 Major depression is a serious health problem affecting more than 5% of the population, with a life-time prevalence of 15-20%.

15 Selective serotonin reuptake inhibitors have produced significant success in treating depression and related illnesses and have become among the most prescribed drugs. They nonetheless have a slow onset of action, often taking several weeks to produce their full therapeutic effect. Furthermore, they are effective in fewer than two-thirds of patients.

20 Serotonin selective reuptake inhibitors (SSRIs) are well known for the treatment of depression and other conditions. SSRIs work by blocking the neuronal reuptake of serotonin, thereby increasing the concentration of serotonin in the synaptic space, and thus increasing the activation of postsynaptic serotonin receptors.

25 However, although a single dose of an SSRI can inhibit the neuronal serotonin transporter which would be expected to increase synaptic serotonin, long-term treatment is required before clinical improvement is achieved.

30 It has been suggested that the SSRIs increase the serotonin levels in the vicinity of the serotonergic cell bodies and that the excess serotonin activates somatodendritic autoreceptors, 5HT_{1A} receptors, causing a decrease in serotonin release in major forebrain areas. This negative feedback limits the increment of synaptic serotonin that can be induced by antidepressants.

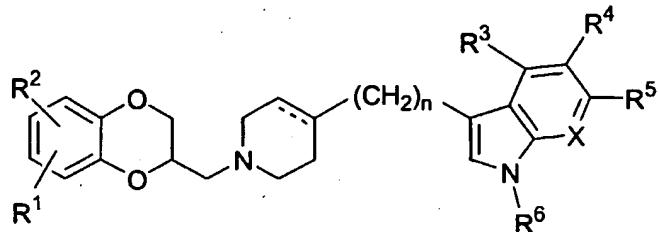
35 A 5HT_{1A} antagonist would limit the negative feedback and should improve the efficacy of the serotonin reuptake mechanism. (Perez, V., et al., *The Lancet*, 349:1594-1597 (1997)). Such a combination therapy would be expected to speed up the effect of the serotonin reuptake inhibitor.

Thus, it is highly desirable to provide improved compounds which both inhibit serotonin reuptake and which are antagonists of the 5HT_{1A} receptor.

Description of the Invention

5

In accordance with this invention, there is provided a group of novel compounds of the formula:



10 wherein

- R¹ and R² are, independently, hydrogen, halogen, cyano, carboxamido, carboalkoxy of two to six carbon atoms, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms; or R¹ and R², taken together, form methylenedioxy, ethylenedioxy or propylenedioxy;
- 15 R³, R⁴, R⁵ and R⁷ are independently selected from hydrogen, halogen, cyano, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms;
- 20 R⁶ is hydrogen or alkyl of 1 to 6 carbon atoms;
- X is CR⁷ or N;
- the dotted line represents an optional double bond; and
- n is an integer 0, 1 or 2;
- 25 or a pharmaceutically acceptable salt thereof.

In some preferred embodiments of the invention R¹ is hydrogen, halo, cyano, carboxamido, trifluoromethyl, amino, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms.

30

In other preferred embodiments of the invention R² is hydrogen, halo, cyano, carboxamido, trifluoromethyl, amino, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms.

5 In still more preferred embodiments of the invention one of R¹ and R² is hydrogen and the other one of R¹ and R² is hydrogen, amino, alkoxy, halogen, or carboxamido and more preferably is alkoxy of one to six carbon atoms attached to position 8 of the benzodioxan moiety.

10 R³, R⁴ and R⁵ are preferably independently selected from hydrogen, halo, cyano, alkyl of one to six carbon atoms, and alkoxy of one to six carbon atoms in some embodiments of the invention. In more preferred embodiments of the invention R³, R⁴ and R⁵ are independently selected from hydrogen, halogen, cyano, and alkoxy.

15 n is preferably 0 or 1.

The optional double bond is preferably present.

20 X is preferably CR⁷. When X is CR⁷, R⁷ is preferably hydrogen, halo, cyano, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms and more preferably hydrogen, halogen, cyano or alkoxy.

25 Still more preferred are compounds wherein R¹ and R² are, independently, hydrogen, halo, cyano, carboxamido, trifluoromethyl, amino, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms; R³, R⁴ and R⁵ are independently selected from hydrogen, halo, cyano, alkyl of one to six carbon atoms, and alkoxy of one to six carbon atoms; and n is an integer 0 or 1.

30 Yet more preferred are those compounds in which R¹ is alkoxy of one to six carbon atoms and is attached to position 8 of the benzodioxan moiety, R² and R⁶ are hydrogen, R³, R⁴ and R⁵ are independently selected from hydrogen, halogen and cyano, X is CR⁷, R⁷ is hydrogen, halo, cyano, n is 0 and the dotted line represents a double bond.

35

This invention relates to both the R and S stereoisomers of the 2-aminomethyl-2,3-dihydro-1,4-benzodioxan, as well as to mixtures of the R and S stereoisomers. Throughout this application, the name of the product of this invention, where the absolute configuration of the 2-aminomethyl-2,3-dihydro-1,4-benzodioxan is not indicated, is intended to embrace the individual R and S enantiomers as well as mixtures of the two. In some preferred embodiments of the present invention the S stereoisomer is preferred.

Where a stereoisomer is preferred, it may in some embodiments be provided substantially free of the corresponding enantiomer. Thus, an enantiomer substantially free of the corresponding enantiomer refers to a compound which is isolated or separated via separation techniques or prepared free of the corresponding enantiomer. Substantially free, as used herein means that the compound is made up of a significantly greater proportion of one stereoisomer. In preferred embodiments the compound is made up of at least about 90% by weight of a preferred stereoisomer. In other embodiments of the invention, the compound is made up of at least about 99% by weight of a preferred stereoisomer. Preferred stereoisomers may be isolated from racemic mixtures by any method known to those skilled in the art, including high performance liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by methods described herein. See, for example, Jacques, et al., Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); Wilen, S.H., et al., Tetrahedron 33:2725 (1977); Eliel, E.L. Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); Wilen, S.H. Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

Alkyl as used herein refers to an aliphatic hydrocarbon chain and includes straight and branched chains such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neo-pentyl, n-hexyl, and isoheptyl which have 1-6 carbon atoms. Lower alkyl refers to alkyl having 1 to 3 carbon atoms.

Alkanamido as used herein refers to the group R-C(=O)-NH- where R is an alkyl group of 1 to 5 carbon atoms.

Alkanoyloxy as used herein refers to the group R-C(=O)-O- where R is an alkyl group of 1 to 5 carbon atoms.

Alkanesulfonamido as used herein refers to the group R-S(O)₂-NH- where R is an alkyl group of 1 to 6 carbon atoms.

Alkoxy as used herein refers to the group R-O- where R is an alkyl group of 1 to 6 carbon atoms.

5 Carboxamido as used herein refers to the group -CO-NH₂.

Carboalkoxy as used herein refers to the group R-O-C(=O)- where R is an alkyl group of 1 to 5 carbon atoms.

Halogen (or halo) as used herein refers to chlorine, bromine, fluorine and iodine.

10 Pharmaceutically acceptable salts are those derived from such organic and inorganic acids as: acetic, lactic, citric, cinnamic, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, oxalic, propionic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, glycolic, pyruvic, methanesulfonic, ethanesulfonic, toluenesulfonic, salicylic, benzoic, and similarly known acceptable acids.

15

Specific compounds of the present invention are:

5-methoxy-3-[4-[1,2,3,6-tetrahydro-1-[2-(2,3-dihydro-[1,4]benzodioxinyl)]-methyl]pyridinyl]indole;

5-fluoro-3-[4-[1,2,3,6-tetrahydro-1-[2-(2,3-dihydro[1,4]benzodioxinyl)]-

20 methyl]pyridinyl]indole;

3-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-2,3-dihydro-benzo-[1,4]dioxin-7-ylamine;

2-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-2,3-dihydro-benzo-[1,4]dioxin-6-ylamine;

25 3-[1-(8-methoxy-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-1H-indole;

2-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-2,3-dihydro-benzo[1,4]dioxin-6-ylamine;

30 3-[1-(8-methoxy-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-1H-indole-5-carbonitrile;

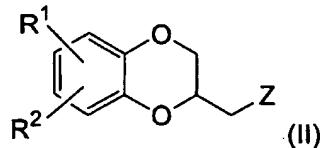
3-[1-(8-methoxy-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-1H-pyrrolo[2,3-b]pyridine;

6-fluoro-3-[1-(8-methoxy-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-1H-indole;

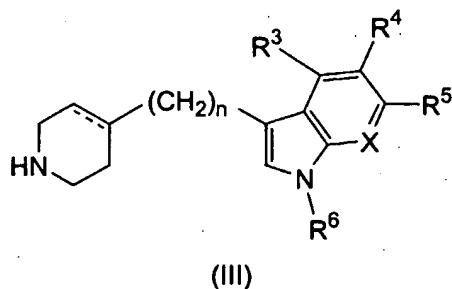
- 3-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-2,3-dihydro-benzo[1,4]-dioxin-5-carboxylic acid amide;
- 3-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-2,3-dihydro-benzo[1,4]dioxin-5-carboxylic acid amide;
- 5 3-(1-[[8-fluoro-2,3-dihydro-1,4-benzodioxin-2-yl]methyl]-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indole;
- 3-(1-[[7-methoxy-2,3-dihydro-1,4-benzodioxin-2-yl]methyl]-1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indole; and
- 10 5-fluoro-3-[1-(8-methoxy-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-1H-indole, and pharmaceutically acceptable salts thereof.

This invention also provides a process for preparing a compound of formula (I) which comprises one of the following:

- a) reacting a compound of formula

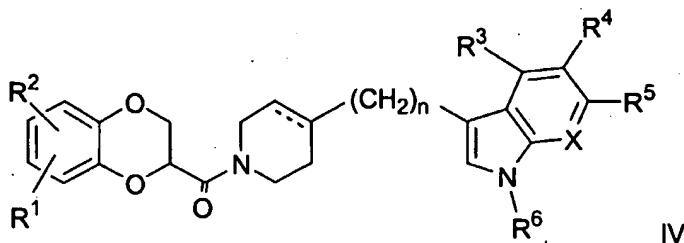


15 wherein R¹ and R² are as defined herein and Z is a leaving group, such as halogen (e.g. Br), alkylsulfonate of 1 to 6 carbon atoms, trifluoromethanesulfonate or benzenesulfonate, in which the benzene ring is optionally substituted with halogen, nitro, trifluoromethyl, cyano, alkyl of 1 to 6 carbon atoms or alkoxy of 1 to 6 carbon atoms; with a compound of formula (III):



wherein the dotted line, n, X, R³, R⁴, R⁵ and R⁶ are as defined herein to give a compound of formula (I); or

(b) reducing an acyl compound of formula (IV):



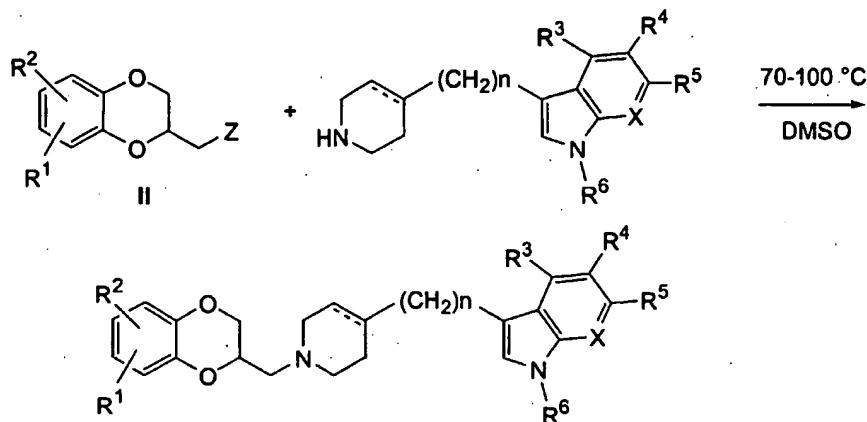
wherein the dotted line, n, X, R¹, R², R³, R⁴, R⁵ and R⁶ are as defined herein to give a compound of formula (I); or

- 5 (c) converting a basic compound of formula (I) to a pharmaceutically acceptable acid addition salt thereof; or
- (d) resolving an isomeric mixture of compounds of formula (I) to isolate an enantiomer of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

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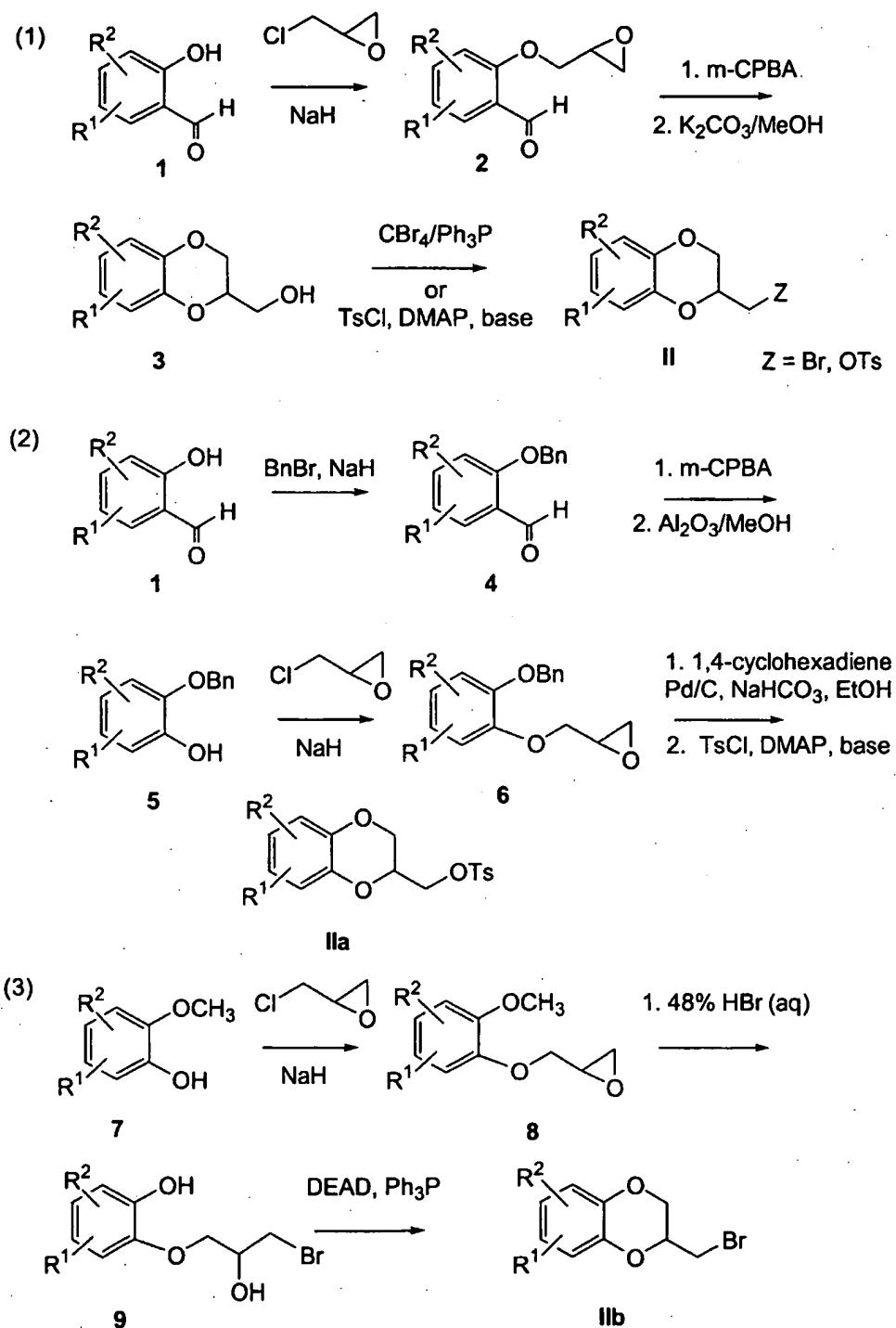
If necessary in any of the processes described herein reactive substituent groups may be protected prior to reaction and removed thereafter.

The compounds of the invention are conveniently prepared by conventional methods. Specifically, the appropriate azaheterocycle may be combined with a suitably substituted benzodioxan methyltosylate or bromide (II) in a solvent such as dimethyl sulfoxide and heated to a temperature of 70-100°C for several hours as illustrated in Scheme I below. Alternatively, the azaheterocycle may be acylated with a suitably substituted benzodioxan carboxylic acid chloride, and the resulting amide reduced to the amine with an appropriate reducing agent such as lithium aluminum hydride or borane/THF. The azaheterocycle may also be

**Scheme I**

combined with a suitably substituted benzodioxan carboxaldehyde in the presence of
5 a reducing agent such as sodium cyanoborohydride.

The azaheterocycles required to prepare the compounds of the invention are known compounds. The benzodioxan methyltosylates and halides are known compounds or they may be prepared from the appropriately substituted salicyl-
10 aldehydes by the method (1) described in Scheme II below. The salicylaldehyde (1) is alkylated with an epihalohydrin or glycidyl arylsulfonate in the presence of a suitable base. The aldehyde moiety (2) is then converted to a phenol by a Baeyer-Villager procedure and cyclization to the benzodioxan methanol effected by treatment with a base such as potassium carbonate. The alcohol (3) is elaborated to a tosylate by
15 treatment with p-toluenesulfonyl chloride and a tertiary amine base or to a bromide by treatment with triphenylphosphine and carbon tetrabromide. Alternatively (2), the substituted salicylaldehyde (1) may be protected with a suitable protecting group such as benzyl to produce (4) and the aldehyde converted to a phenol (5) as described above. Following elaboration of the phenol to the glycidyl ether (6) by treatment with
20 an epihalohydrin or glycidyl arylsulfonate, deprotection and cyclization are effected in a single step via a transfer hydrogenation in the presence of sodium bicarbonate. The bromide or tosylate is prepared as described above to produce II. Or the benzodioxan methylbromide



Scheme II

may be prepared from a suitably substituted guaiacol by procedure (3) shown above in Scheme II. The guiacol (7) is alkylated with a glycidyl arylsulfonate or an epihalohydrin as described above to produce (8). The methyl ether is then cleaved by treatment with 48% HBr; this also converts the epoxide to a bromohydrin (9).

5 Cyclization directly to the benzodioxan methylbromide (IIb) is effected by the Mitsonobu procedure.

The compounds of the invention may be resolved into their enantiomers by conventional methods or, preferably, they may be prepared directly by substitution of 10 (2R)-(-)-glycidyl 3-nitrobenzenesulfonate or tosylate (for the S benzodioxan methylamine) or (2S)-(+)-glycidyl 3-nitrobenzenesulfonate or tosylate (for the R enantiomer) in place of epichlorohydrin in the procedure above.

A protocol similar to that used by Cheetham et. al. (Neuropharmacol. 32:737, 15 1993) was used to determine the affinity of the compounds of the invention for the serotonin transporter. The compound's ability to displace ^3H -paroxetine from male rat frontal cortical membranes was determined using a Tom Tech filtration device to separate bound from free ^3H -paroxetine and a Wallac 1205 Beta Plate[®] counter to quantitate bound radioactivity. K_i 's thus determined for standard clinical 20 antidepressants are 1.96 nM for fluoxetine, 14.2 nM for imipramine and 67.6 nM for zimelidine. A strong correlation has been found between ^3H -paroxetine binding in rat frontal cortex and ^3H -serotonin uptake inhibition.

High affinity for the serotonin 5-HT_{1A} receptor was established by testing the 25 claimed compound's ability to displace [^3H] 8-OHDPAT (dipropylaminotetralin) from the 5-HT_{1A} serotonin receptor following a modification of the procedure of Hall et al., J. Neurochem. 44, 1685 (1985) which utilizes CHO cells stably transfected with human 5-HT_{1A} receptors. The 5-HT_{1A} affinities for the compounds of the invention are reported below as K_i 's.

30 Antagonist activity at 5-HT_{1A} receptors was established by using a ^{35}S -GTP γ S binding assay similar to that used by Lazareno and Birdsall (Br. J. Pharmacol. 109: 1120, 1993), in which the test compound's ability to affect the binding of ^{35}S -GTP γ S to membranes containing cloned human 5-HT_{1A} receptors was determined. Agonists

produce an increase in binding whereas antagonists produce no increase but rather reverse the effects of the standard agonist 8-OHDPAT. The test compound's maximum inhibitory effect is represented as the I_{max} , while its potency is defined by the IC_{50} .

5

The results of the three standard experimental test procedures described in the preceding three paragraphs were as follows:

		5-HT Transporter Affinity	5-HT1A Receptor Affinity	5-HT1A Function
	<u>Compound</u>	<u>KI (nM)</u>	<u>KI (nM)</u>	<u>IC₅₀ (nM) (I_{max})</u>
10	Example 1		27.18	
	Example 2	16.00	68.29	
	Example 3	1.16	30.98	232.0 (96.0)
	Example 4	2.03	131.55	240.0 (90.0)
15	Example 5	0.17	2.85	57.3 (89.3)
	Example 6	0.34	46.73	411.3 (96.7)
	Example 7	1.04	7.95	82.5 (100)
	Example 8	39.00	4.30	26.0 (94.0)
	Example 9	0.60	4.88	272.0 (80.0)
20	Example 10	4.96	64.58	1279.0 (61.0)
	Example 11	3.13	70.57	736.0 (60.0)
	Example 12	49.00	35.51	521.0 (76.0)
	Example 13	40.00	17.29	522.0 (100)
	Example 14	1.79	8.57	70.0 (100)

25

Like the antidepressants fluoxetine, paroxetine and sertraline, the compounds of this invention have the ability to potently block the reuptake of the brain neurotransmitter serotonin. They are thus useful for the treatment of diseases commonly treated by the administration of serotonin selective reuptake inhibitor (SSRI) antidepressants, such as depression (including but not limited to major depressive disorder, childhood depression and dysthymia), anxiety, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder (also known as premenstrual syndrome), attention deficit disorder (with and without hyperactivity), obsessive compulsive disorder (including trichotillomania), social anxiety disorder, generalized anxiety disorder, obesity, eating disorders such as anorexia nervosa,

bulimia nervosa, vasomotor flushing, cocaine and alcohol addiction, sexual dysfunction (including premature ejaculation), and related illnesses. Moreover, the compounds of this invention have potent affinity for and antagonist activity at brain 5-HT_{1A} serotonin receptors. Recent clinical trials employing drug mixtures (eg, 5 fluoxetine and pindolol) have demonstrated a more rapid onset of antidepressant efficacy for a treatment combining SSRI activity and 5-HT_{1A} antagonism (Blier and Bergeron, 1995; F. Artigas et. al., 1996; M. B. Tome et. al., 1997). The compounds of the invention are thus exceedingly interesting and useful for treating depressive illnesses.

10

Thus the present invention provides methods of treating, preventing, inhibiting or alleviating each of the maladies listed above in a mammal, preferably in a human, the methods comprising providing a pharmaceutically effective amount of a compound of this invention to the mammal in need thereof.

15

Also encompassed by the present invention are pharmaceutical compositions for treating or controlling disease states or conditions of the central nervous system comprising at least one compound of Formula I, mixtures thereof, and/or pharmaceutical salts thereof, and a pharmaceutically acceptable carrier therefore.

20

Such compositions are prepared in accordance with acceptable pharmaceutical procedures, such as described in *Remingtons Pharmaceutical Sciences*, 17th edition, ed. Alfonoso R. Gennaro, Mack Publishing Company, Easton, PA (1985). Pharmaceutically acceptable carriers are those that are compatible with the other ingredients in the formulation and biologically acceptable.

25

The compounds of this invention may be administered orally or parenterally, neat or in combination with conventional pharmaceutical carriers. Applicable solid carriers can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc,

sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

- 5 Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, 10 buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and 15 polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.
- 20 Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.
- 25 Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets, capsules, powders, solutions, suspensions, emulsions, granules, or suppositories. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or 30 sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

35 The amount provided to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, and

the state of the patient, the manner of administration, and the like. In therapeutic applications, compounds of the present invention are provided to a patient already suffering from a disease in an amount sufficient to cure or at least partially ameliorate the symptoms of the disease and its complications. An amount adequate to
5 accomplish this is defined as a "therapeutically effective amount." The dosage to be used in the treatment of a specific case must be subjectively determined by the attending physician. The variables involved include the specific condition and the size, age and response pattern of the patient. Generally, a starting dose is about 5 mg per day with gradual increase in the daily dose to about 150 mg per day, to
10 provide the desired dosage level in the human.

Provide as used herein means either directly administering a compound or composition of the present invention, or administering a prodrug, derivative or analog which will form an equivalent amount of the active compound or substance within the
15 body.

The present invention includes prodrugs of compounds of Formula I. "Prodrug", as used herein means a compound which is convertible *in vivo* by metabolic means (e.g. by hydrolysis) to a compound of Formula I. Various forms of prodrugs are known in the art, for example, as discussed in Bundgaard, (ed.), Design of Prodrugs, Elsevier (1985); Widder, et al. (ed.), Methods in Enzymology, vol. 4, Academic Press (1985); Krogsgaard-Larsen, et al., (ed). "Design and Application of Prodrugs, Textbook of Drug Design and Development, Chapter 5, 113-191 (1991), Bundgaard, et al., Journal of Drug Deliver Reviews, 8:1-38(1992), Bundgaard, J. of
20 Pharmaceutical Sciences, 77:285 et seq. (1988); and Higuchi and Stella (eds.)
25 Prodrugs as Novel Drug Delivery Systems, American Chemical Society (1975).

The following examples illustrate the production of representative compounds of this invention.

EXAMPLE 15-Methoxy-3-[4-[1,2,3,6-tetrahydro-1-[2-(2,3-dihydro[1,4]benzodioxinyl)]methyl]pyridinyl]indole

5 2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl 4-methylbenzenesulfonate (1.10 g, 3.44 mmole) was dissolved in a mixture of dimethylformamide/tetrahydrofuran (1:1 v/v, 30 mL) and 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole (0.80 g, 3.5 mmole) added, followed by sodium bicarbonate (1.0 g), and the mixture was refluxed under nitrogen for 18 hours. The solvent was removed under vacuum and the residue
10 partitioned between 400 mL each of methylene chloride and water. The layers were separated and the organic phase was washed with water and saturated sodium chloride solution, dried over magnesium sulfate and evaporated to a foam (0.70 g). A sample was converted to the oxalate salt, m.p. 120°C (dec.).

Elemental Analysis for: C₂₃H₂₄N₂O₃ • C₂H₂O₄ • 0.50 H₂O

15 Calc'd: C, 63.15; H, 5.72; N, 5.89
Found: C, 63.04; H, 5.61; N, 5.84

EXAMPLE 25-Fluoro-3-[4-[1,2,3,6-tetrahydro-1-[2-(2,3-dihydro[1,4]benzodioxinyl)]methyl]pyridinyl]indole

20 2,3-Dihydro-benzo[1,4]dioxin-2-ylmethyl 4-methylbenzenesulfonate (1.18 g, 3.5 mmole) was dissolved in a mixture of dimethylformamide/tetrahydrofuran (1:1 v/v, 30 mL) and 5-fluoro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole (0.60 g, 2.8 mmole)
25 added, followed by sodium bicarbonate (1.0 g), and the mixture was refluxed under nitrogen for 18 hours. The solvent was evaporated under vacuum, and the residue partitioned between 400 mL each of water and methylene chloride. The layers were separated and the organic phase was washed with water and saturated aqueous sodium chloride solution, dried over magnesium sulfate and filtered. The filtrate was
30 evaporated under vacuum to yield a solid (0.50 mg). A portion of this residue was converted to the oxalate salt, m.p. 145°C (dec.).

Elemental Analysis for: C₂₂H₂₁FN₂O₂ • C₂H₂O₄ • 0.50 H₂O

Calc'd: C, 62.20; H, 5.22; N, 6.04
Found: C, 62.39; H, 5.08; N, 6.06

EXAMPLE 33-[4-(1H-Indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-2,3-dihydro-
benzo[1,4]dioxin-7-ylamine

5

(2R)-2-(Bromomethyl)-7-nitro-2,3-dihydro-benzo[1,4]dioxin (1.0 g, 3.6 mmole) was dissolved in DMSO (50 mL) and 3-(1,2,3,6)-tetrahydro-4-pyridinyl-1H-indole (0.60 g, 3.0 mmole) added and the mixture was heated under nitrogen at 80°C for four hours. The reaction mixture was cooled and added to water (100 mL). The mixture 10 was extracted with methylene chloride. The organic layer was washed with water and saturated aqueous sodium chloride solution, dried over anhydrous potassium carbonate, and filtered. The filtrate was evaporated in vacuum to give 1.0 g of the nitro intermediate as an amorphous residue. This was dissolved in methanol and added to a refluxing mixture of hydrazine hydrate (1.25 mL, mmole) and Raney 15 Nickel (1.25 g) in methanol (15 mL) and the reaction mixture was refluxed for 30 minutes. The hot reaction mixture was filtered through celite and the filtrate evaporated in vacuum. The residue was crystallized from isopropanol, giving a light yellow solid, m.p. 204-206°C.

Elemental Analysis for: C₂₂H₂₃N₃O₂ • 0.25 H₂O
20 Calc'd: C, 72.21; H, 6.47; N, 11.48
Found: C, 72.48; H, 6.38; N, 11.51

EXAMPLE 42-[4-(1H-Indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-2,3-dihydro-
benzo[1,4]dioxin-6-ylamine

25

(2R)-2-(Bromomethyl)-6-nitro-2,3-dihydro-benzo[1,4]dioxin (1.0 g, 3.6 mmole) was dissolved in DMSO (50 mL) and 3-(1,2,3,6)-tetrahydro-H-pyridinyl-1H-indole (0.60 g, 3.0 mmole) added. The solution was heated at 80°C under nitrogen for 16 hours 30 and then allowed to cool to room temperature and poured into water (100 mL). The product was extracted using methylene chloride (100 mL). This extract was washed with water, and saturated sodium chloride solution, dried over anhydrous potassium carbonate, filtered and evaporated in vacuum, yielding 3-[1-[(2S)-6-nitro-2,3-dihydro-

benzo[1,4]dioxo-2-yl)-1,2,3,6-tetrahydro-pyridin-4-yl]-1H-indole as a yellow solid, m.p. 183-185 °C (1.2 g, 83 %).

Elemental Analysis for: C₂₂H₂₁N₃O₄ • 0.25 H₂O

Calc'd: C, 66.74; H, 5.47; N, 10.61

5 Found: C, 66.57; H, 5.24; N, 10.37

To a refluxing solution of hydrazine hydrate (1.25 mL, 25 mmole) in methanol (20 mL) containing Raney Nickel (1.25 g) was added a warm methanol solution of 3-[1-(2S)-6-nitro-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl]-1,2,3,6-tetrahydro-pyridin-4-yl]-1H-indole (1.0 g, 2.6 mmole) under nitrogen. The reaction mixture was refluxed for 45 minutes, during which time all reacting solids dissolved. The reaction mixture was filtered through celite while hot, and the filtrate evaporated in vacuum. The solid obtained was recrystallized from isopropanol to give 200 mg of the (S)-enantiomer of the title compound as a light yellow solid, m.p. 199-200°C.

15 Elemental Analysis for: C₂₂H₂₃N₃O₂

Calc'd: C, 73.11; H, 6.41; N, 11.63

Found: C, 72.82; H, 6.39; N, 11.51

EXAMPLE 5

20 3-[1-(8-Methoxy-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-1,2,3,6-tetrahydro-
pyridin-4-yl]-1H-indole

(2R)-8-Methoxy-2,3-dihydro-benzo[1,4]dioxin-2-yl)methyl-4-methylbenzene-sulfonate (1.1 g, 3.1 mmole) was dissolved in a mixture of dimethylformamide/tetrahydrofuran (1:1 v/v, 50 mL) and 3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole (0.60 g 1.6 mmole) added, followed by sodium bicarbonate (1.0 g). The reaction mixture was refluxed under nitrogen for 18 hours, then cooled and concentrated in vacuum. The residue was partitioned between 400 mL each of water and ethyl acetate. The layers were separated. The organic phase was washed with water and saturated aqueous sodium chloride solution, dried over anhydrous potassium carbonate and evaporated to a foam (1.0 g). Trituration with ether yielded a solid which was recrystallized from boiling chloroform/methanol (1:1 v/v) to give 0.40 g (40%) of the (S)-enantiomer of the title compound as an off-white solid one-quarter hydrate, m.p. 203-205°C.

Elemental Analysis for: C₂₃H₂₄N₂O₃ • 0.25 H₂O

Calc'd: C, 72.51; H, 6.48; N, 7.35

Found: C, 72.27; H, 6.34; N, 7.30

5

EXAMPLE 6

2-[4-(5-Fluoro-1H-Indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-2,3-dihydro-benzo[1,4]dioxin-6-ylamine

(2R)-2-(Bromomethyl)-6-nitro-2,3-dihydro-benzo[1,4]dioxin (2 g, 7.3 mmole)

10 was dissolved in DMSO (50 mL) and 5-fluoro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H indole (1.0 g, 4.6 mmole) added. The reaction mixture was heated at 90°C under nitrogen for 18 hours. The reaction mixture was cooled, poured into water (100 mL) and the product extracted using methylene chloride. The organic phase was washed with water and saturated aqueous sodium chloride solution, dried over anhydrous potassium carbonate and filtered. The filtrate was evaporated in vacuum to give a solid (0.90 g). The solid was added to a refluxing solution of hydrazine hydrate (1.25 mL, 25 mmole) in methanol (20 mL) containing Raney Nickel (1.25 g) under nitrogen. The reaction mixture was refluxed for 45 minutes, during which time the reagents dissolved. The catalyst was removed by filtration through celite and the filtrate evaporated in vacuum. The residue was crystallized from methylene chloride to give 0.30 g of the (S)-enantiomer of the title product as a white solid (m.p. 172-174 °C) containing 0.06 equivalents of methylene chloride.

Elemental Analysis for: C₂₂H₂₂FN₃O₂ • 0.06 CH₂Cl₂

Calc'd: C, 68.91; H, 5.80; N, 10.93

25 Found: C, 68.51; H, 5.70; N, 10.70

EXAMPLE 7

3-[1-(8-Methoxy-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-1H-indole-5-carbonitrile]

30

3-(1,2,3,6-Tetrahydro-4-pyridinyl)1H-indole-5-carbonitrile (0.70 g, 3.1 mmole)

and [(2R)-8-methoxy-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl-4-methylbenzenesulfonate (0.40 g, 1.1 mmole) were dissolved in a mixture of dimethylformamide/tetrahydrofuran (1:1 v/v, 50 mL) and sodium bicarbonate (1.0 g) added. The reaction mixture was refluxed under nitrogen for 18 hours. The solvent was evaporated in

vacuum and the residue partitioned between 400 mL each of methylene chloride and water. The organic phase was separated, washed with water and saturated aqueous sodium chloride solution, dried over magnesium sulfate and filtered. The filtrate was evaporated in vacuum to give a solid which was purified by column chromatography
5 on silica gel. Elution with 2% methanol in chloroform, concentration of the product fractions in vacuum and treatment of an ethereal solution of the residue with 4 N isopropanolic HCl gave the (S)-enantiomer of the title compound (250 mg, 54%) as a yellow solid hydrochloride, one-quarter hydrate, m.p. 235-238 °C.

Elemental Analysis for: C₂₄H₂₃N₃O₃ • HCl • 0.25 H₂O
10 Calc'd: C, 65.15; H, 5.58; N, 9.50
Found: C, 64.96; H, 5.59; N, 9.09

EXAMPLE 8

3-[1-(8-Methoxy-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-1,2,3,6-tetrahydro-
15 pyridin-4-yl]-1H-pyrrolo[2,3-b]pyridine

[(2R)-8-Methoxy-2,3-dihydro-benzo[1,4]dioxin-2-yl]methyl 4-methylbenzene-sulfonate (0.27 g, 0.79 mmole) and 3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-pyrrolo-[2,3-b]pyridine (0.17 g, 0.87 mmole) were dissolved in DMSO (15 mL). Triethylamine
20 (0.22 mL) was added and the reaction mixture heated at 80 °C under nitrogen for 4 hours. The reaction mixture was poured into 400 mL of water and extracted with methylene chloride. The extract was washed with water and 1 N sodium hydroxide solution, dried over Na₂SO₄ and filtered. The filtrate was evaporated in vacuum and the residue was chromatographed on silica gel using 10% methanol in methylene
25 chloride as eluant. Upon evaporation of the product fractions in vacuum, 0.22 g (53%) of the (S)-enantiomer of the title compound was obtained as a pale yellow solid, m.p. 207-210°C.

Elemental Analysis for: C₂₂H₂₃N₃O₃ • 0.6 H₂O
30 Calc'd: C, 68.06; H, 6.28; N, 10.82
Found: C, 68.05; H, 6.06; N, 10.66

EXAMPLE 9**6-Fluoro-3-[1-(8-methoxy-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-1H-indole**

5 [(2R)-8-Methoxy-2,3-dihydro-benzo[1,4]dioxin-2-yl]methyl 4-methylbenzenesulfonate (0.30 g, 0.86 mmole), 6-fluoro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole (0.60 g, 2.7 mmole) and sodium bicarbonate (0.80 g) were added to a mixture of dimethylformamide/tetrahydrofuran (1:1 v/v, 20 mL) and the reaction mixture was refluxed under nitrogen for 18 hours. The solvent was evaporated and the residue
10 partitioned between 400 mL each of water and methylene chloride. The layers were separated and the methylene chloride solution was washed with water and saturated aqueous sodium chloride solution, dried over anhydrous potassium carbonate and filtered. The filtrate was evaporated in vacuum and the residue crystallized from chloroform containing 3% methanol, giving 0.23 g (68%) of the (S)-enantiomer of the
15 title compound as an off-white solid, m.p. 184-185°C.

Elemental Analysis for: C₂₃H₂₃FN₂O₃ • 0.25 H₂O.

Calc'd: C, 69.25; H, 5.94; N, 7.02

Found: C, 69.26; N, 5.88; N, 7.10

20

EXAMPLE 10**3-[4-(1H-Indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-2,3-dihydro-benzo[1,4]dioxine-5-carboxylic acid amide**

25 (2R)-8-(Aminocarbonyl)-2,3-dihydro-benzo[1,4]dioxin-2-yl)methyl 4-methylbenzenesulfonate (0.60 g, 1.15 mmole) and 3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole (0.68 g, 3.4 mmole) were dissolved in DMSO (6 mL) and the mixture heated at 80°C under nitrogen for 18 hours. The reaction mixture was poured into water. The mixture was extracted with ethyl acetate and washed with water and saturated aqueous sodium chloride solution, dried over magnesium sulfate and filtered. The
30 filtrate was evaporated under vacuum to give an oil (1.6 g). Chromatography on silica gel using 30% isopropanol in methylene chloride as eluant gave a solid which was recrystallized from methylene chloride to give 0.1 g (15 %) of the (S)-enantiomer of the title compounds as a white solid, m.p. 175-178°C.

Elemental Analysis for: C₂₃H₂₃N₃O₃ • 0.50 H₂O

Calc'd: C, 69.33; H, 6.07; N, 10.55

Found: C, 69.40; H, 5.98; N, 10.43

5

EXAMPLE 11

3-[4-(5-Fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-2,3-dihydro-benzo[1,4]dioxine-5-carboxylic acid amide

(2R)-8-(Aminocarbonyl)-2,3-dihydro-benzo[1,4]dioxin-2-yl)methyl-4-methylbenzenesulfonate (0.60 g, 1.65 mmole) and 5-fluoro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole (0.75 g, 3.4 mmole) were dissolved in DMSO (6 mL) and the mixture heated at 80°C under nitrogen for 24 hours. The reaction mixture was poured into water, and the product extracted with ethyl acetate. The extract was washed with water and saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated in vacuum to give an orange oil (1.0 g). Chromatography on silica gel using 30% isopropanol in methylene chloride as eluant gave the title compound as a solid, which was further purified on another column using 1% methanol in chloroform as eluant. Combination of the product fractions and evaporation in vacuum resulted in the isolation of 0.15 g (23%) of the (S)-enantiomer of the title compound as a yellow solid, m.p. 195-197°C.

Elemental Analysis for: C₂₃H₂₂FN₃O₃

Calc'd: C, 67.80; H, 5.44; N, 10.31

Found: C, 67.52; H, 5.66; N, 10.23

25

EXAMPLE 12

3-(1-[[8-Fluoro-2,3-dihydro-1,4-benzodioxin-2-yl]methyl]-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

[(2R)-8-Fluoro-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl 4-methylbenzenesulfonate (1.2 g, 3.5 mmole) was dissolved in a mixture of dimethylformamide-/tetrahydrofuran (1:1 v/v, 30 mL) and 3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole (0.60 g, 3.0 mmole) added, followed by the addition of sodium bicarbonate (0.60 g, 7.1 mmole) and the mixture refluxed under nitrogen for 18 hours. The solvent was evaporated in vacuum, and the residue partitioned between 400 mL each of methylene chloride and water. The organic phase was dried over magnesium sulfate

and filtered. The filtrate was evaporated and the residue chromatographed on silica gel using 4% methanol in chloroform as eluant. The product fractions were combined and concentrated in vacuum to give 0.20 g (16%) of the (S)-enantiomer of the title compound as a yellow solid, m.p. 174-177°C.

5 Elemental Analysis for: C₂₂H₂₁FN₂O₂ • 0.25 H₂O

Calc'd: C, 71.62; H, 5.15; N, 7.59

Found: C, 71.69; H, 5.64; N, 7.57

EXAMPLE 13

10 3-(1-[(7-Methoxy-2,3-dihydro-1,4-benzodioxin-2-yl)methyl]-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

[(2R)-7-Methoxy-2,3-dihydro-benzo[1,4]dioxin-2-yl)methyl 4-methylbenzenesulfonate (1.5 g, 4.3 mmole) was dissolved in a mixture of dimethyl-formamide/tetrahydrofuran

15 (1:1 v/v, 30 mL) and 3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indole (0.80 g, 4.0 mmole) added, followed by sodium bicarbonate (1.0 g), and the mixture was refluxed under nitrogen for 18 hours. The solvent was removed under vacuum and the residue partitioned between 400 mL each of methylene chloride and water. The layers were separated and the organic phase was washed with water and saturated sodium

20 chloride solution, dried over potassium carbonate and filtered. The filtrate was evaporated to a foam (1.6 g). Chromatography on silica gel using 4% methanol in chloroform as eluant gave 0.20 g of the (S)- enantiomer of the title compound as a yellow solid, m.p. 166-168°C.

Elemental Analysis for: C₂₃H₂₄N₂O₃ • 0.25 H₂O

25 Calc'd: C, 72.52; H, 6.48; N, 7.35

Found: C, 72.34; H, 5.42; N, 7.14

EXAMPLE 14

30 5-Fluoro-3-[1-(8-methoxy-2,3-dihydro-benzo[1,4]dioxin-2-yl)methyl]-1,2,3,6-tetrahydro-pyridin-4-yl]-1H-indole

[(2R)-8-Methoxy-2,3-dihydro-benzo[1,4]dioxin-2-yl)methyl 4-methylbenzene-sulfonate (0.40 g, 1.1 mmole) was dissolved in a mixture of tetrahydrofuran/dimethylformamide (1:1 v/v, 25 mL) and 5-fluoro-3-(1,2,3,6-tetrahydro-4-

pyridinyl)-1H-indole (0.30 g, 1.4 mmole) added, followed by the addition of sodium bicarbonate (0.60 g), and the mixture refluxed for 18 hrs. The solvent was removed under vacuum, and the residue partitioned between 400 mL each of methylene chloride and water. The organic phase was separated, washed with water and 5 saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated to a glassy solid (1.0 g). A small portion was converted to the oxalate salt, m.p. 154-156°C.

Elemental Analysis for: C₂₃H₂₃FN₂O₃ • C₂H₂O₄ • 0.50 H₂O

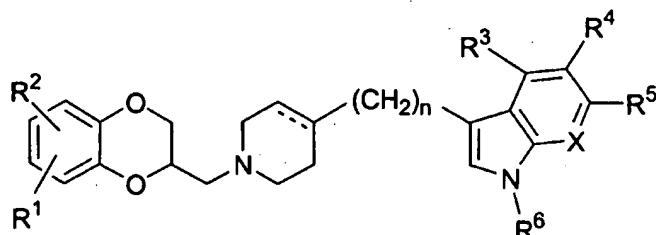
Calc'd: C, 60.85; H, 5.31; N, 5.68

10 Found: C, 60.39; H, 4.97; N, 5.52

CLAIMS

What is claimed is:

- 5 (1) A compound of formula I



wherein

R¹ and R² are, independently, hydrogen, halogen, cyano, carboxamido, carboalkoxy of two to six carbon atoms, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms; or R¹ and R², taken together, form methylenedioxy, ethylenedioxy or propylenedioxy;

10 R³, R⁴, R⁵ and R⁷ are independently selected from hydrogen, halogen, cyano, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms;

15 R⁴ is hydrogen or alkyl of 1 to 6 carbon atoms;

R⁷ is CR⁷ or N;

the dotted line represents an optional double bond; and

n is an integer 0, 1 or 2;

or a pharmaceutically acceptable salt thereof.

20 (2) A compound according to Claim 1 wherein R¹ is hydrogen, halo, cyano, carboxamido, trifluoromethyl, amino, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms.

(3) A compound according to Claim 1 or Claim 2 wherein R² is hydrogen, halo, cyano, carboxamido, trifluoromethyl, amino, alkyl of one to six carbon atoms or alkoxy of one to six carbon atoms.

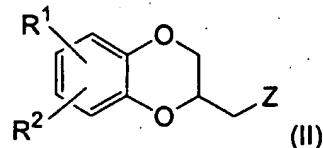
- (4) A compound according to Claim 1 wherein one of R¹ and R² is hydrogen and the other one of R¹ and R² is hydrogen, amino, alkoxy, halogen, or carboxamido.
- (5) A compound according to Claim 4 wherein R¹ is alkoxy of one to six carbon atoms and is attached to position 8 of the benzodioxan moiety.
- (6) A compound according to any one of Claims 1 to 5 wherein R³, R⁴ and R⁵ are independently selected from hydrogen, halo, cyano, alkyl of one to six carbon atoms, and alkoxy of one to six carbon atoms.
- 10 (7) A compound according to any one of Claims 1 to 6 wherein n is 0 or 1.
- (8) A compound of Claim 1 in which R¹ and R² are, independently, hydrogen, halo, cyano, carboxamido, trifluoromethyl, amino, alkyl of one to six carbon atoms or 15 alkoxy of one to six carbon atoms; R³, R⁴ and R⁵ are independently selected from hydrogen, halo, cyano, alkyl of one to six carbon atoms, and alkoxy of one to six carbon atoms; n is an integer 0 or 1; or a pharmaceutically acceptable salt thereof.
- (9) A compound according to any one of Claims 1 to 8 wherein X is CR⁷ and R⁷ 20 is hydrogen, halo, cyano, alkyl of one to six carbon atoms, or alkoxy of one to six carbon atoms.
- (10) A compound of Claim 1 in which R¹ is alkoxy of one to six carbon atoms and is attached to position 8 of the benzodioxan moiety, R² and R⁴ are hydrogen, R³, R⁴ 25 and R⁵ are independently selected from hydrogen, halo and cyano, X is CR⁷, R⁷ is hydrogen, halo, cyano, n is 0 and the dotted line represents a double bond; or a pharmaceutically acceptable salt thereof.
- (11) The compound of Claim 1 which 5-methoxy-3-[4-[1,2,3,6-tetrahydro-1-[2-(2,3-dihydro[1,4]benzodioxinyl)]methyl]pyridinyl]indole or a pharmaceutically acceptable 30 salt thereof.
- (12) The compound of Claim 1 which is 5-fluoro-3-[4-[1,2,3,6-tetrahydro-1-[2-(2,3-dihydro[1,4]benzodioxinyl)]methyl]pyridinyl]indole or a pharmaceutically acceptable 35 salt thereof.

- (13) The compound of Claim 1 which is 3-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-2,3-dihydro-benzo[1,4]dioxin-7-ylamine or a pharmaceutically acceptable salt thereof.
- 5 (14) The compound of Claim 1 which is 2-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-2,3-dihydro-benzo[1,4]dioxin-6-ylamine or a pharmaceutically acceptable salt thereof.
- 10 (15) The compound of Claim 1 which 3-[1-(8-methoxy-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-1H-indole or a pharmaceutically acceptable salt thereof.
- 15 (16) The compound of Claim 1 which 2-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-2,3-dihydro-benzo[1,4]dioxin-6-ylamine or a pharmaceutically acceptable salt thereof.
- 20 (17) The compound of Claim 1 which 3-[1-(8-methoxy-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-1H-indole-5-carbonitrile or a pharmaceutically acceptable salt thereof.
- 25 (18) The compound of Claim 1 which 3-[1-(8-methoxy-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-1H-pyrrolo[2,3-b]pyridine or a pharmaceutically acceptable salt thereof.
- 30 (19) The compound of Claim 1 which 6-fluoro-3-[1-(8-methoxy-2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-1H-indole or a pharmaceutically acceptable salt thereof.
- (20) The compound of Claim 1 which is 3-[4-(1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-2,3-dihydro-benzo[1,4]dioxin-5-carboxylic acid amide or a pharmaceutically acceptable salt thereof.

- (21) The compound of Claim 1 which is 3-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-ylmethyl]-2,3-dihydro-benzo[1,4]dioxin-5-carboxylic acid amide or a pharmaceutically acceptable salt thereof.
- 5 (22) The compound of Claim 1 which is 3-(1-{[8-fluoro-2,3-dihydro-1,4-benzodioxin-2-yl]methyl}-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole or a pharmaceutically acceptable salt thereof.
- 10 (23) The compound of Claim 1 which is 3-(1-{[7-methoxy-2,3-dihydro-1,4-benzodioxin-2-yl]methyl}-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole or a pharmaceutically acceptable salt thereof.
- 15 (24) The compound of Claim 1 which is 5-fluoro-3-[1-(8-methoxy-2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl)-1,2,3,6-tetrahydro-pyridin-4-yl]-1H-indole or a pharmaceutically acceptable salt thereof.
- 20 (25) A method of treating a subject suffering from a condition selected from the group consisting of depression, anxiety, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, attention deficit disorder, obsessive compulsive disorder, social anxiety disorder, generalized anxiety disorder, obesity, eating disorders, vasomotor flushing, cocaine and alcohol addiction, and sexual dysfunction, which comprises providing to the subject suffering from said condition, a therapeutically effective amount of a compound of formula I as claimed in any one of claims 1 to 24 or a pharmaceutically acceptable salt thereof.
- 25 (26) The method of Claim 25 wherein the condition is depression.
- (27) The method of Claims 25 wherein the condition is obsessive compulsive disorder, panic attacks, generalized anxiety disorder or social anxiety disorder.
- 30 (28) The method of any one of Claims 25 to 27 wherein the subject is a human.
- (29) A pharmaceutical composition comprising a compound of formula I as claimed in any one of claims 1 to 24 or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

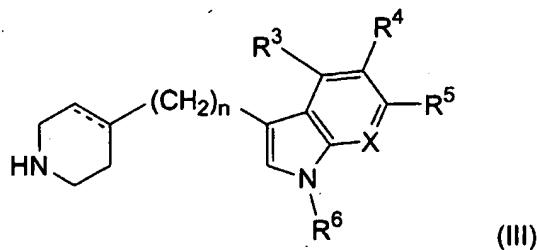
(30) A process for preparing a compound according to Claim 1 which comprises one of the following:

- a) reacting a compound of formula



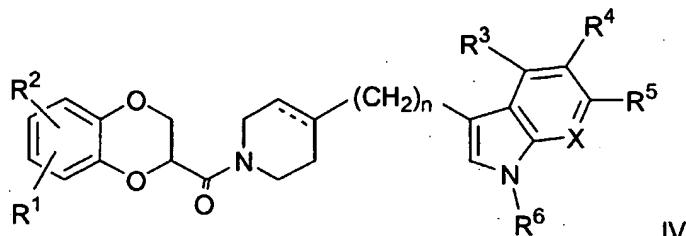
5 wherein R¹ and R² are as defined in claim 1 and Z is a leaving such as halogen (e.g. Br), alkylsulfonate of 1 to 6 carbon atoms, trifluoromethanesulfonate or benzenesulfonate, in which the benzene ring is optionally substituted with halogen, nitro, trifluoromethyl, cyano, alkyl of 1 to 6 carbon atoms or alkoxy of 1 to 6 carbon atoms;

10 with a compound of formula (III):



wherein the dotted line, n, X, R³, R⁴, R⁵ and R⁶ are as defined in claim 1 to give a compound of formula (I); or

- (b) reducing an acyl compound of formula (IV):



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wherein the dotted line, n, X, R¹, R², R³, R⁴, R⁵ and R⁶ are as defined in claim 1 to give a compound of formula (I) as claimed in claim 1; or

- (c) converting a basic compound of formula (I) to a pharmaceutically acceptable acid addition salt thereof; or
 20 (d) resolving an isomeric mixture of compounds of formula (I) to isolate an enantiomer of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

	International Application No PCT/US 02/12843
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A. CLASSIFICATION OF SUBJECT MATTER				
IPC 7	C07D405/14	C07D471/04	A61K31/404	A61K31/437
A61P25/24				

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 02 072587 A (WYETH) 19 September 2002 (2002-09-19) page 52 -page 62; claims 1-44 ---	1-30
Y	WO 01 14330 A (SOLVAY PHARMACEUTICALS B.V.) 1 March 2001 (2001-03-01) page 21 -page 24; claims 1-7 ---	1-30
Y	WO 00 15636 A (F. HOFFMANN-LAROCHE AG) 23 March 2000 (2000-03-23) page 67 -page 74; claims 1-25 ---	1-30
Y	EP 1 092 715 A (ADIR ET COMPANIE) 18 April 2001 (2001-04-18) page 12 -page 15; claims 1-14 ---	1-30 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the International search

26 September 2002

Date of mailing of the International search report

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INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 02/12843

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 55695 A (AMERICAN HOME PRODUCTS CORPORATION) 4 November 1999 (1999-11-04) page 13 -page 15; claims 11-15 ---	1-30
Y	EP 0 529 462 A (MERCK PATENT GESELLSCHAFT MIT BESCHRÄNKTER HAFTUNG) 3 March 1993 (1993-03-03) page 14 -page 16; claims 1-7 ---	1-30
Y	EP 0 376 607 A (H.LUNDBECK A/S) 4 July 1990 (1990-07-04) page 14 -page 17; claims 1-8 -----	1-30

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/12843

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 25 and 26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/12843

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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CORRECTED VERSION

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471/04, A61K 31/404, 31/437, A61P 25/24

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(25) Filing Language: English

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(74) Agents: BARRETT, Rebecca, R.; Wyeth, Patent Law Department, Five Giralda Farms, Madison, NJ 07940-0874 et al. (US).

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Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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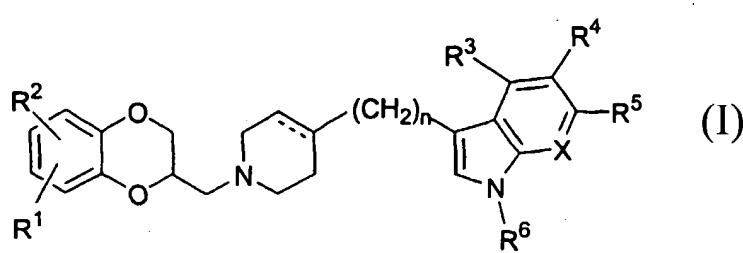
(15) Information about Correction:

see PCT Gazette No. 48/2002 of 28 November 2002, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTIDEPRESSANT AZAHETEROCYCLIMETHYL DERIVATIVES OF 2,3-DIHYDRO-1,4-BENZODIOXAN

WO 02/085896 A1



(57) Abstract: Compounds of the formula (I), useful for the treatment of depression and other conditions such as obsessive compulsive disorder, panic attacks, generalized anxiety disorder, sexual dysfunction, eating disorders, addictive disorders caused by ethanol or cocaine abuse and related illnesses.